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(54) **Polymeric liquid dressing for skin.**

(57) There is described a polymeric formulation suitable for applying to the skin in a thin layer to form a protective coating thereon, which formulation comprises a sterile liquid formulation comprising an ethylene/vinyl acetate copolymer which preferably includes paraffin wax, and an organic liquid solvent for said copolymer.

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# POLYMERIC LIQUID DRESSING FOR SKIN

The invention relates to the art of liquid polymeric dressings for skin.

## Background of the Invention

Liquid polymeric preparations that can be sprayed on or otherwise thinly applied to the intact or injured skin as protective coatings and/or as carriers for medicaments have been suggested for many years. They are often called "spray-on bandages" or "liquid bandages". Such preparations are disclosed, for instance, by Von Fieandt et al., U.S. Patent No. 3,269,903, who disclose dressings made of hydroxyalkyl methacrylate polymers, and Gleichenhagen et al., U.S. Patent No. 3,987,000, who disclose isobutene/acrylic copolymers as protective coatings for wounds. Other U.S. patents that disclose wound coverings made of various types of polymeric materials include the following:

Wang No. 4,793,336
Gould et al. No. 3,377,516
Hofeditz et al. No. 4,552,138
Pellico No. 4,291,025
King No. 3,419,006
Korol No. 4,563,184
Gurney No. 3,880,158

Commercially available liquid bandages include the following formulations:

1. Pyroxylin solution, oil of cloves, 8-hydroxyquinoline, and ethanol;
2. benzethonium chloride, dyclonine hydrochloride, and ethanol;
3. Cellulose acetate butyrate, 2-ethylhexyl diphenyl phosphate, and acetone;
4. A polymer that appears to be partially hydrolyzed vinyl chloride/vinyl acetete copolymer and a sebacic acid based polyester that is used as a polymeric plasticizer for the vinyl resin, modified maleic rosin ester, ethyl acetate, and acetone; and
5. Ethoxyethyl methacrylate polymer, tetramethyl thiuram disulfide, and ethyl acetate.

This invention relates to a polymeric formulation that can be applied to the skin in a liquid formulation which, upon evaporation of the liquid carrier in the formulation, acts as a protective coating for the intact or injured skin and can serve as a carrier for one or more medicaments. The formulation of the invention has the useful property of developing excellent adhesion to the skin, but the coating formed from the formulation has a non-sticky outer surface that does not tend to pick up dirt or to adhere to dressings. The protective film formed by the formulation of the invention is durable; it adheres to the skin at least as long as other commercially available liquid bandages, but it is more comfortable because it is compliant and more conformable to the skin. The liquid bandage of the invention also has the valuable property of having little or no tendency to sting when it is applied to the intact or injured skin.

## Brief Summary of the Invention

The invention provides a polymeric formulation suitable for applying to the skin in a thin layer to form a protective coating thereon, which formulation comprises a sterile liquid comprising an ethylene/vinyl acetate copolymer which preferably contains paraffin wax, and an organic liquid solvent for said copolymer.

## The Prior Art

Pospischil, in U.S. Patent No. 3,803,300, mentions that paraffin can be used as a base for an "ointment foil" for application to the skin. The ointment foil is prepared by drying an oil-in-water type emulsion to form a film with sufficient strength to be handled, and thereafter this film is applied to the skin.

## Detailed Description of the Invention

The polymeric formulation of the invention that is used to form a protective coating on the intact or

injured skin comprises an ethylene/vinyl acetate copolymer that preferably also contains a paraffin wax, and a liquid organic carrier. Optionally, the formulation may contain medicaments such as antibiotics and other anti-microbial agents, anti-fungal agents, corticosteroids, derivatives of retinoic acid, growth factors, non-steroidal anti-inflammatory agents, peroxides such as benzoyl peroxide, ultraviolet light absorbers, analgesics, mixtures of two or more of the above, and the like.

The polymer used in the invention is ethylene/vinyl acetate ("EVA") copolymer. The copolymer has a polymerized vinyl acetate content effective to impart adequate solvent solubility at room temperature and to improve the conformability of the copolymer to skin. For instance, the copolymer usually contains from about 30 to about 60 weight percent of polymerized vinyl acetate, the remainder being polymerized ethylene. The EVA copolymers employed in the invention usually have molecular weights such that they have inherent viscosities within the range of from about 0.3 to about 0.7 dl/gm, tested at a concentration of 0.1 gm/dl in methyl ethyl ketone at 25 ° C. The ethylene/vinyl acetate copolymers used in the invention are available commercially.

Paraffin wax is preferably used in the invention to increase the modulus of elasticity of the protective film formed by the polymeric composition of the invention. The incorporation of crystalline paraffin wax in the EVA copolymer makes the protective film less rubbery and stretchy. The paraffin wax is used in an amount effective to impart to the protective coating of the invention aesthetics, the desired surface characteristics, and balance of modulus, flexibility, and conformability, without adversely affecting the adhesion of the film to the skin. Usually, the desired amount of paraffin will be found in the range of from about 2 to 25, and preferably 5 to 15, weight percent, based on the combined weight of the EVA copolymer and the wax. Routine experimentation will suffice to determine the exact proportions of wax that is desired in individual cases.

The crystalline paraffin wax used in the invention is defined as a wax having a melting point greater than about 45 ° C and is composed primarily of low molecular weight hydrocarbon, e. g., low molecular weight polyethylene.

The polymeric formulation of the invention contains an organic liquid vehicle that is a solvent for the EVA copolymer and preferably for the the paraffin wax, which is a preferred component of the formulation. A mixture of a $C_{5-8}$ alkane or cycloalkane such as hexane, cyclohexane, heptane, octane, or mixture thereof, and the like with a $C_{3-6}$ lower alkanol such as isopropyl alcohol or n-butanol has been found to be useful as the organic vehicle. Isopropyl alcohol is the preferred lower alkanol. Because the organic solvent mixture is predominantly composed of hydrocarbons, and is therefore hydrophobic, the liquid bandage of the invention has a reduced tendency to cause stinging during application to tissue. The formulation can be prepared by standard techniques, such as by mixing the paraffin wax and the EVA copolymer (in powdered or pellet form) in the alkane until the EVA copolymer is fully swollen, warming the mixture to a moderately elevated temperature below the boiling point of the alkane (e.g., 40-60 ° C), and then adding enough lower alkanol to cause the EVA copolymer to dissolve in the mixture. Suitable proportions of alkanol to alkane will usually be found in the range of from about 1:24 to about 1:7, by weight. The proportion of solids (EVA copolymer plus wax) to organic vehicle is not narrowly critical, and can vary from about 10 to about 35 weight percent solids, based on total weight of the formulation.

The formulation can be sterilized by conventional means such as by filtration and irradiation.

The formulation described above is suitable for applying to the unbroken or to the injured skin by brushing, spraying, or the like. By adding a propellant, the formulation may be formulated for application as an aerosol.

Example 1

Preparation of 100 gms of a liquid bandage is done by first mixing 19.8 gms of EVA copolymer (40 wt% vinyl acetate content, inherent viscosity = 0.53 dl/gm, tested at a concentration of 0.1 g/dl in methyl ethyl ketone at 25 ° C, and 2.2 gms of paraffin wax (mp 53-56 ° C) with 74.9 gms of hexane until the EVA copolymer is fully swollen. The mixture is warmed to about 50 ° C and 3.1 gms of isopropyl alcohol are added under continuous agitation to obtain a clear solution. The liquid polymer solution thus obtained is suitable for application to the skin by brushing or spraying. The film on the skin that is formed after the organic solvent mixture has evaporated has good adhesion to the skin and has a non-sticky surface.

Example 2

By procedures similar to that described above, a series of bandage formulations containing various medicaments were prepared. Table I, below, presents the proportions of the ingredients in each formulation. It is noted that a small amount of water is employed in the solvent system for several of the formulations in order to aid in the dissolution of the medicaments. When water is employed, it may be necessary to increase the proportion of lower alkanol in order to ensure a single phase formulation.

TABLE I

| | COMPOSITION (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) |
| EVA | 19.37 | 18.57 | 16.30 | 18.92 | 18.92 | 18.81 | 18.83 | 17.98 |
| Parrafin Wax | 2.152 | 2.063 | 1.883 | 2.103 | 2.112 | 2.090 | 2.093 | 1.997 |
| hexane | 73.28 | 70.25 | 72.45 | 71.60 | 71.93 | 71.18 | 71.26 | 68.01 |
| IPA* | 3.033 | 6.565 | 6.770 | 4.302 | 3.841 | 5.797 | 4.757 | 6.356 |
| water | 0 | 0.328 | 0.539 | 0.956 | 0.960 | 0 | 0.951 | 3.632 |
| Gramicidin (Sigma Lot# 48F-0071) | 0.005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Polymixin B Sulphate (Sigma Lot# 18F-0030) | 0 | 0.026 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bacitracin (Sigma Lot# 97F-0747) | 0 | 0.131 | 0.156 | 0 | 0 | 0 | 0 | 0 |
| Gentamycin Sulphate (Sigma Lot# 67F-0171) | 0 | 0 | 0 | 0.002 | 0 | 0 | 0 | 0 |
| Chlorhexidine diacetate (Sigma Lot# 57F-0542) | 0 | 0 | 0 | 0 | 0.021 | 0 | 0 | 0 |
| Tretinoin (Retin A) (Ortho Lot # 288048) | 0 | 0 | 0 | 0 | 0 | 0.020 | 0 | 0 |
| EGF* Cake (Lot # I027E97) Contains 4.96% EGF | 0 | 0 | 0 | 0 | 0 | 0 | 0.003 | 0.018 |
| total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Notes: | | | | | | | | |

* "IPA" represents isopropyl alcohol
* "EGF" represents Epidermal Growth Factor

The liquid bandage of the invention can also be applied as a protective covering for experimental wounds, including full thickness wounds, on animals. It is often necessary to create experimental wounds on animals to test the efficacy of surgical devices such as sutures and staples and therapeutic agents, including antimicrobials and growth factors. The liquid bandage can be very useful for forming a compliant protective polymeric film covering for such wounds. This covering provides least discomfort to the animal and decreases its tendency to dislodge the protective coating. The covering of this invention presents a substantial improvement over the high Tg, less compliant, hardly conformable methacryalte polymers that are available to the animal testing community.

In a pilot study, the liquid bandage described in Example 1 was applied to full thickness wounds on a few rats. Upon drying, the applied solution formed a thin film covering the wound and the surrounding intact skin. The film bandage was well adherent to intact skin but non-adherent to the wound. The experimental animals were observed for a period of seven days. During the first three days, the protective film remained in place with only some lifting of the edges. No infection or inflammatory response was noted on or around the wound site. The film covering also remained occlusive during this time period, as evidenced by the absence of leakage of any wound exudate. Other details of the liquid bandage functionality study are noted in the surgical report given below.

LIQUID BANDAGE:

EXPERIMENTAL PROCEDURE FOR BANDAGING FULL THICKNESS WOUNDS IN THE RAT

SUMMARY

Six mature Long-Evans rats were prepared and presented for aseptic surgery. An 8 mm full thickness dermal wound was created on the dorsal surface of the cervical region. The liquid bandage was applied to the wound and surrounding skin and allowed to dry. The rats were observed daily for 5 to 7 days.

The liquid bandage was acceptable for bandaging 8 mm full thickness dermal wounds in the rat for up to 3 days. The bandage could be reapplied and resulted in decreasing area of the wound at 5 and 7 days similar to that seen with BIOCLUSIVE dressing.

CONCLUSIONS

The liquid bandage of this invention was acceptable for bandaging 8 mm full thickness dermal wounds in the rat for up to 3 days. The bandage could be reapplied and resulted in decreasing area of the wound at 5 and 7 days similar to that seen with BIOCLUSIVE dressing.

## Claims

1. A polymeric formulation suitable for applying to the skin in a thin layer to form a protective, adherent coating thereon, which coating has a non-sticky outer surface, which formulation comprises an ethylene/vinyl acetate copolymer and an organic liquid solvent for said copolymer.
2. A formulation of Claim 1 wherein said formulation further comprises paraffin wax.
3. The formulation of claim 1 or claim 2 wherein said organic liquid solvent comprises a mixture of a lower alkane or cycloalkane and a lower alkanol.
4. The formulation of claim 3 wherein the organic liquid solvent comprises a mixture of hexane and isopropyl alcohol.
5. The formulation of any preceding claim wherein said formulation further comprises a medicament.
6. The formulation of any of claims 1 to 4 wherein said formulation further comprises an agent selected from the group consisting of antimicrobial agents, analgesics, anti-inflammatory agents, growth factors, derivatives of retinoic acid, peroxides, ultraviolet light absorbers, and mixtures thereof.
7. The formulation of any of claims 1 to 4 wherein said formulation further comprises a medicament selected from the group consisting of antibiotics, anti-fungal agents, corticosteroids, tretinoin, epidermal growth factor, non-steroidal anti-inflammatory agents, benzoyl peroxide, and mixtures thereof.
8. A method for applying a protective coating to the skin which method comprises applying the sterile polymeric formulation of any of claims 1 to 4 to the skin in a thin layer and permitting the organic liquid solvent to evaporate.
9. A formulation according to any of claims 1 to 4, for use as a medical dressing.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 90 30 7785

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| X | GB-A-2 188 844 (ROHM PHARMA GMBH)<br>* the whole document * | 1,5-9 | A 61 L 25/00<br>A 61 K 9/70 |
| A | WO-A-8 809 185 (KURT BURGHART ET AL.)<br>* claims 1-18 * | 1-9 | |
| A | US-A-3 476 853 (BERNARD JATUL ET AL.)<br>* the whole document * | 1-9 | |
| A | EP-A-0 288 336 (LABORATOIRES D'HYGIENE ET DE DIETETIQUE L.H.D.)<br>* claims 1-11 * | 1-9 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K
A 61 L
A 61 M

The present search report has been drawn up for all claims

| Place of search | Date of completion of search | Examiner |
|---|---|---|
| The Hague | 30 October 90 | SIATOU E |

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document